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REMARKS

Claims 44-56 are under examination. New claims 57-59 have been added. Support for new claim 57 can be found in original claims 9-12. Support for new claims 58 and 59 can be found in original claims 13 and 14. Accordingly, these new claims do not raise an issue of new matter, and entry thereof is respectfully requested.

REJECTION UNDER 35 U.S.C. § 103

The rejection of claims 44-56 under 35 U.S.C. § 103 over He et al., Bioorg. Med. Chem. Lett. 4:2845-2850 (1994) in view of Traxler et al., J. Med. Chem. 34:2328-2337 (1991), and Rossman et al., The Enzymes Volume XI, Part A, 3rd ed., P. Boyer, ed., Academic Press, New York (1975), and Radzicka et al., Methods Enzymol. 249:284-303 (1995), is respectfully traversed. Applicant respectfully maintains that the claims are unobvious over He et al., alone or in combination with Traxler et al. and/or Rossman et al. and/or Radzicka et al.

Section 2142 of the M.P.E.P states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

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Applicant respectfully maintains that at least two of the three criteria required to establish a *prima facie* case of obviousness have not been met. First, it is respectfully submitted that there is no suggestion or motivation to modify the reference or combine reference teachings. Secondly, it is respectfully submitted that there is no reasonable expectation of success based on the cited references. Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established.

As discussed in the response previously mailed June 18, 2003, He et al. describes bi-substrate inhibitors of protein kinase C (PKC). There is no teaching or suggestion in He et al. of identifying inhibitors for any enzyme other than PKC. Accordingly, He et al. provides no motivation to obtain inhibitors of any kinase other than PKC, let alone a dehydrogenase or enzyme that binds the cofactor nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP).

The reference by Traxler et al. describes synthesis of a series of sulfonylbenzoyl-nitrostyrene derivatives as bisubstrate type inhibitors of the EGF receptor tyrosine kinase. Like He et al., Traxler et al. provides no teaching or suggestion to modify the reference to obtain inhibitors of kinases other than EGF receptor tyrosine kinase. Despite the lack of motivation to combine these references, even if, arguendo, one combined the teachings of He et al. and Traxler et al., at best one would expect to make kinase inhibitors, not the claimed method for identifying a population of bi-ligands to dehydrogenases. Therefore, the combination of He et al. and Traxler et al. provides no reasonable expectation of success for obtaining the claimed methods for identifying a population of

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bi-ligands to dehydrogenases since such a combination of references may, at best, provide kinase inhibitors.

The Office Action asserts that Radzicka et al. describes transition state and multisubstrate inhibitors and that Rossman et al. describes a structural similarity between dehydrogenases and kinases. However, as discussed in the previous response, the description in Rossman et al. of a similarity between kinases and dehydrogenases refers to a nucleotide binding domain but does not refer to a structural similarity between these different enzymes which carry out completely different enzymatic reactions, phosphotransfer and oxidation-reduction, respectively. These differences in enzymatic activity are reflected in the different structures and chemical functionalities involved in the respective enzymatic activities (Exhibit 1 of previous response mailed June 18, 2003). Furthermore, Applicant respectfully disagrees with the assertion on page 6 of the Office Action that "Rossman et al teach that there is structural similarity between dehydrogenases and kinases, thus the application of the method of He et al to the dehydrogenase family would be obvious to one of ordinary skill." Given the well known differences between kinases and dehydrogenases, it is respectfully submitted that one skilled in the art would have had no motivation to apply the method described in He et al. for identifying PKC inhibitors to dehydrogenases to obtain the claimed methods or any expectation that using the method of He et al. would have resulted in the claimed method of identifying a population of bi-ligands to dehydrogenases or enzymes that bind NAD or NADP.

In the Office Action, a reference describing protein kinase C inhibitors (He et al.) has been combined with a reference that describes EGF receptor tyrosine kinase inhibitors (Traxler et al.), a review article on transition state and

multisubstrate inhibitors (Radzicka et al.) and a review article that indicates that it is "most probable" that the nucleotide binding domain of phosphoglycerate kinase has structural similarity to the nucleotide binding domain of lactate dehydrogenase (Rossman et al.), and this combination of references is alleged to render the claimed methods obvious. Applicants respectfully submit that it is only with the hindsight benefit of Applicants' disclosure that the combination of He et al., Traxler et al., Radzicka et al. and Rossman et al. can be advanced. It is well established that Applicant's disclosure cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed (In re Laskowski, 871 F.2d 115, 117; 10 USPQ 2d 1397, 1398 (Fed. Cir. 1989)). Hindsight cannot be used to resolve the questions of obviousness (Orthopedic Equipment Co., Inc. v United States 702 F.2d 1005, 1012 (Fed. Cir. 1983)):

[t]he difficulty which attaches to all honest attempts to answer this question [non-obviousness] can be attributed to the strong temptation to rely on hindsight while undertaking this evaluation. It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.

Applicants respectfully submit that the only way the disclosures of He et al., Traxler et al., Radzicka et al. and Rossman et al. can be read to result in the claimed methods is with benefit of Applicants' disclosure. Such hindsight application of Applicants' disclosure is clearly improper. Absent the teachings in Applicants' disclosure, there is no teaching or suggestion in any of the cited references to motivate one skilled in the art to combine the cited references. Furthermore, there is no reasonable expectation of success for

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obtaining the claimed methods based on the cited references. Absent such a teaching or suggestion, it is respectfully submitted that the claimed methods are unobvious over He et al., Traxler et al., Radzicka et al., and/or Rossman et al. Accordingly, Applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112

The rejection of claims 44-56 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description is respectfully traversed. Applicant respectfully maintains that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed.

Applicant notes that a previous written description rejection under 35 U.S.C. § 112, first paragraph, was withdrawn in the Office Action mailed December 18, 2002. The only difference between the previously pending claims, which were indicated to be sufficiently supported in the specification, and the presently pending claims is the recitation of "dehydrogenase" (claims 44 and 52) and an enzyme family that "binds the cofactor nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate (claims 47 and 52). These claims are identical to previously pending claims 9, 11 and 12, except that they are limited to one member of the Markush groups of claims 11 and 12. It is unclear why claims that were previously indicated to be sufficiently supported by the written description in the specification and are directed to a narrower embodiment that was explicitly recited in the claims that were previously indicated to be sufficiently supported

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would now be considered to lack sufficient written description. Nevertheless, Applicant addresses this issue below.

The Office Action indicates that "[A] description of a compound in terms of its function fails to distinguish the compound from others having the same activity or function." It is respectfully pointed out that the claims are directed to methods for identifying a bi-target ligand. Nevertheless, the claims do recite terms such as "cofactor or mimic thereof," "nicotinamide adenine dinucleotide," and "nicotinamide adenine dinucleotide phosphate," which clearly provide a structural and functional activity of the bi-ligands to be identified by the claimed methods. The claimed methods are directed to identifying a population of bi-ligands to dehydrogenases or enzymes that bind NAD or NADP, and Applicant maintains that such methods are sufficiently described by the teachings in the specification.

The specification teaches a method for identifying a population of bi-ligands to a receptor (page 15, line 29, to page 16, line 15). The specification further teaches that a receptor can be an enzyme such as a dehydrogenase or an enzyme that binds NAD or NADP (page 11, lines 6-7; page 12, lines 31-33). The specification additionally teaches methods for identifying a bi-ligand to a receptor such as a dehydrogenase or enzyme that binds NAD or NADP (pages 29-46). Therefore, it is respectfully submitted that the specification provides sufficient description and guidance for the claimed methods.

The Office Action indicates on page 10, first complete paragraph, that adequate disclosure, like enablement, requires representative examples which provide reasonable assurance to one skilled in the art that compounds falling within the scope possess utility and demonstrate that Applicant was in possession

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of the claimed invention. The Office Action further asserts that “[T]he more unpredictable the art the greater the showing required (e.g. by “representative examples”) for both enablement and adequate disclosure.” Applicant’s representative is not aware of the precedent for such an assertion with respect to written description and would appreciate being provided with the relevant authority so that the case law can be reviewed and responded to appropriately.

Applicant maintains that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant was in possession of the claimed methods for identifying a population of bi-ligands to dehydrogenases or an enzyme that binds NAD or NADP at the time the application was filed. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 44-56 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicant respectfully maintains that the claims are clear and definite.

In the Office Action, claims 44-56 are indicated to be indefinite as being incomplete for “omitting essential cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections,” referring to MPEP § 2172.01. The Office Action asserts that the omitted structural relationships are the structures of the compounds, for example, the linker structure and linkage sites, that bring about the claimed binding activity specific to dehydrogenases or enzymes that bind NAD or NADP.

Applicant respectfully disagrees with the assertion that the claims omit essential cooperative relationships of elements. The method claims specifically recite that the linker

is attached to a common ligand, which is a cofactor or mimic thereof, that the linker has sufficient length and orientation to direct a second ligand to a substrate binding site of a dehydrogenase or enzyme that binds NAD or NADP, that a second ligand is linked to the linker, and that the population of bi-ligands generated by linking a common ligand and second ligand via a linker is screened for binding to a dehydrogenase or enzyme that binds NAD or NADP. It is respectfully submitted that the relationship between the linker and ligands is explicitly recited in the claims and that the relationship between these elements to bring about specific binding activity to a dehydrogenase or enzyme that binds NAD or NADP is also explicitly recited.

With respect to the reference to MPEP § 2172.01, the section related to a rejection under § 112, second paragraph, refers to In re Venezia, 530 F.2d 956, 189 USPQ 149 (CCPA 1976) and In re Collier, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). It is respectfully pointed out that the issue in these cases was the relationship between a kit and a coaxial cable, respectively, and language in the claims related to the use of elements of the kit and coaxial cable. The CCPA found that language regarding the use of the components of the coaxial cable did not provide a positive recitation between two elements (In re Collier), whereas the components of the kit were viewed as definite (In re Venezia). It is respectfully submitted that the issues raised in In re Collier and In re Venezia are distinguishing features relevant to comparing the method claims of the present invention, which clearly recite the relationship between elements, as discussed above, and the apparatus and kit with tangible structural features at issue in In re Collier and In re Venezia.

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Applicant respectfully submits that claims 44-56 are clear and definite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

Respectfully submitted,

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